

Remarks

Claims 1-16 and 31-45 have been cancelled. Claims 17, 25 and 30 have been amended. No new matter is added with these amendments. New claims 46-58 have been added. Support for these new claims is found in paragraph 81 of the specification and in the claims as originally filed. By this amendment, claims 17-30 and 46-58 are pending.

Summary of Interview with Examiner

Applicant and Applicant's representatives wish to thank the Examiner for her time and consideration during the personal interview with the Applicant's representatives, John McDonald and Stephen MacDonald, on August 8, 2006. During the interview, Applicant's representatives discussed prospective amendments to the claims and the differences between the claimed method and the cited prior art (Gerra et al. *Current Therapeutic Research*, 1991; and Nutt et al. *Alcohol and Alcoholism*, 1993).

As indicated on the Interview Summary, Applicant's representatives explained that the present invention differs from the prior art in that the present invention, as claimed, is directed to treating alcohol dependency and not to treating alcohol withdrawal. The two conditions differ greatly including different modes of evaluation criteria.

Double Patenting

Claims 17-45 were provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1, 3-6, 8-13 and 28 of co-pending application serial number 11/111,435. Claims 31-45 have been cancelled rendering moot their rejection. Applicant respectfully requests the deferral of this rejection until such time that allowable subject matter is found in both applications.

Rejections under 35 U.S.C. §112, first paragraph (enablement)

Claims 30 and 44 have been rejected under 35 U.S.C. §112, first paragraph as lacking enablement for the term “eliminating desire to use alcohol”. Applicant respectfully traverses this rejection. Claim 44 has been cancelled, rendering moot this rejection. Applicant has amended claim 30 to remove the term “eliminating” and therefore respectfully requests withdrawal of this rejection.

Rejections under 35 U.S.C. §103

Claims 17-26, 29, 31-40, 43 and 45 have been rejected under 35 U.S.C. §103(a) as being obvious over Gerra et al. (*Current Therapeutic Research*, 1991, hereinafter “Gerra”) in view of Nutt et al., (*Alcohol and Alcoholism*, 1993, hereinafter “Nutt”). Applicant respectfully traverses the rejection.

The Examiner asserts that Gerra and Nutt in combination disclose the claimed methods. It is important to note that alcohol withdrawal syndrome and alcohol dependency are two different conditions. The amended claims are directed to methods of treating alcohol dependency with flumazenil. The present invention, as claimed, reduces cravings and the desire to drink alcohol, thereby reducing dependency. Gerra and Nutt teach methods of treating alcohol withdrawal symptoms and not alcohol dependency. Alcohol dependency develops over time. The most severe drinking behavior includes prolonged binges of drinking with associated mental or physical complications, and behavioral changes related to alcohol consumption. In contrast, alcohol withdrawal refers to a group of physical symptoms that may occur from suddenly stopping the use of alcohol after chronic or prolonged ingestion. Not everyone who stops drinking experiences withdrawal symptoms. Symptoms of withdrawal may include elevated temperature, increased blood pressure, rapid heart rate,

First Response to Office Action

Serial No. 10/621,229

Page 7 of 13

restlessness, anxiety, psychosis, seizures, and sometimes even death. The enclosed article by Bender (*Psychiatric Times*, 1995, Vol XII(9)) cites a study that “evidenced clear differentiation between withdrawal symptoms and drug craving” (Exhibit A, Bender, p. 3).

The distinction between alcohol withdrawal syndrome and alcohol dependency may also be shown by the different evaluation criteria for dependency and withdrawal. Withdrawal is evaluated using a CIWA score as a reflection of the symptoms of withdrawal whereas dependency is evaluated using the DSM IV behavioral criteria. Withdrawal symptoms are short-term, typically lasting 1-2 days after initiation of abstinence, while dependency is characterized by physical and behavioral symptoms that are more long term, sometimes lasting years. Treating alcohol withdrawal does not treat alcohol dependency. Withdrawal treatments are typically for short term treatment of withdrawal symptoms while dependency and potential to return to alcohol use persists. The table below summarizes the distinction between the two.

Withdrawal	Dependency
Evaluated with CIWA ¹ score: <u>Symptoms:</u> <ul style="list-style-type: none">• seizures• delirium tremens• weakness• sweats• nausea• depression• insomnia	Evaluated using DSM IV ² criteria: <u>Symptoms:</u> <ul style="list-style-type: none">• impaired judgment• impaired control over drug use• tolerance• withdrawal upon abstaining• imbibe more than intended• unsuccessful efforts to stop• taken to avoid withdrawal• time spent in obtaining the substance replaces social, occupational or recreational activities• continued use despite adverse consequences
Short term (1-2 days)	Long term (weeks to years)
Reduction of withdrawal symptoms does not cause abstinence or reduction in cravings	Reduction in dependency causes reduction in use, abstinence, reduction in desire for use of substance, cravings, anxiety

Neither Gerra or Nutt, alone or in combination, disclose actions of flumazenil on alcohol dependency. The cited references did not even evaluate symptoms of dependency. There is no indication that following the teachings of Gerra or Nutt would result in reduced use, sobriety and/or abstinence from alcohol, and lack of desire for further alcohol consumption. Conversely, the Applicant has shown that flumazenil, in effective concentrations and dosing protocols, can be used to reduce or to stop compulsive usage. The specification teaches at paragraph 81 that the majority of patients reported decreased anxiety and desire to drink alcohol. Gerra and Nutt fail to teach, suggest or provide any motivation to derive a treatment resulting in a reduction in the desire to drink alcohol and a method to

¹ J Clin Psychopharmacol, 1981, 1:382-387

² DSM-IV, American Psychiatric Association, Washington D.C., 1994,

treat alcohol dependency. Therefore, the claimed methods are not obvious in view of Gerra and Nutt.

Furthermore, the Examiner states that Gerra discloses administering flumazenil in a dose of 2 mg/day divided into four doses every six hours and that Nutt discloses a single 2 mg dose of flumazenil infused over 1 minute. The Examiner concludes that the two references therefore collectively disclose the claimed range of flumazenil for treating alcohol dependency. This is incorrect for several reasons. Firstly, Gerra divides a 2 mg/day dosage of flumazenil over a 24 hour period while Nutt administers a single dose in one minute. Nutt fails to divide the dose of flumazenil. Secondly, neither author, alone or in combination, teaches, suggests or provides motivation, to administer low doses of flumazenil to obtain an effective amount to treat dependency. As stated above, neither reference discloses treatment of dependency. Thirdly, the Examiner indicates that it would be obvious to optimize the time intervals and dosage of flumazenil over a broad range because dramatically varying dosages is routine in order to obtain toxicology data. Applicant respectfully asserts that flumazenil is a known drug with established toxicology data. There is no motivation from the cited prior art to experiment with different administration dosages and timing intervals between 1 and 24 hours because the toxicology of flumazenil is already known. This experimentation would be undue.

There is no teaching, suggestion or motivation in the cited prior art that sequential low doses of flumazenil, as claimed, would be effective in treating alcohol dependency. Absent the teachings of the specification, one of ordinary skill would fail to arrive at the claimed methods in view of the deficient disclosures of Gerra and Nutt. The claimed method uses effective dosages of flumazenil to treat underlying alcohol dependency that are effective to

reduce “anxiety and the desire to drink alcohol” in the majority of patients. In comparison with the dosage and method of Gerra, the low dosage and the method of administering flumazenil in the present invention result in low toxicity and side effects, and treats alcohol dependency. These results are unexpected and could not be derived from the prior art that only teaches treatment of alcohol withdrawal symptoms.

Furthermore, the cited references and the background of the specification teach that use of flumazenil to treat alcohol dependency has been discouraged due to previous reports showing variability and lack of efficacy of flumazenil treatment. The cited references did not even evaluate symptoms of longer term dependency. One of ordinary skill in the art was only sporadically able to reduce withdrawal symptoms and was unable to treat alcohol dependency. This accounts for the lack of clinical trials and published articles using flumazenil for treating alcohol withdrawal symptoms for the last ten years since Nutt was published. As a specific example, Nutt states that the actions of flumazenil were highly variable and in some instances, symptoms actually worsened. (Nutt, page 339, line 13). The specification teaches that these articles have favored the abandonment of flumazenil to treat alcohol withdrawal symptoms and have not even contemplated use of flumazenil to treat alcohol dependency.

In view of the preceding arguments, the claimed methods of treating alcohol dependency are not obvious in view of Gerra and Nutt. These references alone or in combination fail to teach, suggest or provide motivation to derive Applicant’s claimed method. Absent the teachings of the present specification, one of ordinary skill would fail to arrive at the claimed methods. Applicant respectfully requests withdrawal of this rejection.

First Response to Office Action

Serial No. 10/621,229

Page 11 of 13

Claims 27-28, 41 and 42 have been rejected under 35 U.S.C. §103(a) as being obvious over Gerra et al. (Current Therapeutic Research, 1991) in view of Nutt et al., (Alcohol and Alcoholism, 1993) in further view of Opitz (U.S. Patent No. 5,519,017). Applicant respectfully traverses the rejection. Gerra and Nutt have been described above.

Opitz

Opitz is cited for the teaching that drugs such as clomethiazole, piracetam and disulfiram may be used to control the influence of alcohol and alcoholism. Opitz fails to make up for the deficiencies of Gerra and Nutt in treating alcohol dependency with flumazenil and therefore fails to render the claimed methods obvious. Neither Gerra, Nutt or Opitz, alone or in combination, provide any teaching, suggestion or motivation to derive Applicant's claimed method. Applicant respectfully requests withdrawal of this rejection.

Claims 17-26, 29, 31-40, 43 and 45 have been rejected under 35 U.S.C. §103(a) as being obvious over Gerra et al. (Current Therapeutic Research, 1991) in view of Nutt et al., (Alcohol and Alcoholism, 1993) in further view of Aguirre et al. (Alcohol, 1990). Applicant respectfully traverses the rejection. Gerra and Nutt have been described above.

Aguirre

Aguirre is cited for the teaching that decreased β -endorphin causes alcohol consumption. The Examiner combines the teaching of Aguirre with the statement by Gerra that flumazenil increases β -endorphin levels and concludes that administering a drug such as flumazenil that raises β -endorphin levels will necessarily treat alcoholism. Applicant respectfully disagrees. The Examiner concludes that because β -endorphin levels are decreased in alcoholics, raising β -endorphin levels must treat dependency. This logic

implies that a decrease in β -endorphin levels must cause alcoholism. This logic also implies that increasing beta-endorphin levels in alcoholics will reduce dependency on alcohol.

There is no indication from Aguirre that decreases in β -endorphin levels are necessarily caused by alcoholism, nor is there any teaching or suggestion that a decrease in β -endorphin is the sole cause of alcoholism. A decrease in β -endorphin levels may simply be a co-incident marker of alcoholism, a complex disease. To conclude anything further would be an overstatement of the data presented in Aguirre. Absent the teachings of the present specification, there is no teaching or suggestion that would provide the skilled artisan with a reasonable expectation that flumazenil would be an effective drug to treat the complex disorder of alcohol dependency. The Applicant has demonstrated that low doses of flumazenil, administered sequentially, reduces the desire to drink alcohol in patients with alcohol dependency. There is no reason to derive this invention from the deficient teachings of Aguirre, Gerra and Nutt. As such, Applicant asserts that the claimed method could not be obvious in view of the teachings of these references, alone or in combination. Applicant respectfully requests withdrawal of this rejection.

Conclusion

Applicant submits that the pending claims define novel and patentable subject matter and provide a complete response to the Office Action. Accordingly, Applicant respectfully requests allowance of these claims. No additional fees are believed due, however, the Commissioner is hereby authorized to charge any deficiencies which may be required, or credit any overpayment, to Deposit Account Number 11-0855.

Early and favorable consideration is earnestly solicited. If the Examiner believes any informalities remain in the application that can be resolved by telephone interview, a telephone call to the undersigned attorney is earnestly solicited.

Allowance of claims 17-30 and 46-58 is respectfully solicited.

Respectfully submitted,

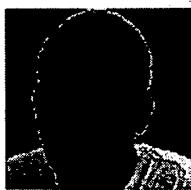


John K. McDonald, Ph.D.

Reg. No. 42,860

KILPATRICK STOCKTON LLP
1100 Peachtree Street
Suite 2800
Atlanta, Georgia 30309-4530
Tel. (404) 745-2470
Fax. (404) 541-3297
General Fax. (404) 815-6555

Attorney Docket No: 55979-0100US (314586)



He can't afford his medicat

[Newsletter](#) [Editorial Board](#) [Contribute](#) [About PT](#) [Subscribe](#) [Contact Us](#)[Dementia](#) | [Bipolar Disease](#) | [Depression](#) | [Clinical Scales](#) | [All Topics](#)[Author Index](#) | [Classifieds](#) | [CME Credit](#) | [Magazine Archives](#)[Become a n
PsychiatricTimes](#)

Breaking News From MedPage Today

[Diets High in Copper and Fats Linked to Cognitive Decline](#) 08/15/2006[Never-Marrieds Have the Highest Risk of Early Death](#) 08/10/2006[Elevated Blood Sugar Sours Older Women's Wits](#) 08/10/2006[Increased Antidepressant Suicide Risk Not Found for Adults](#) 08/08/2006[Ketamine May Give 'Almost Instantaneous' Relief for Severe Depression](#) 08/07/2006[More News!](#)

Classifieds

[California Practice Opportunities](#)[Nationwide Practice Opportunities](#)[Fellowships and Residency](#)

Browse by Topic

[Anxiety and Panic Disorders](#)[Bipolar Disease](#)[Children and Adolescents](#)[Dementia](#)[Dependency](#)[Depressive Disorders](#)[Eating Disorders](#)[Electroconvulsive Therapy](#)

Drug Craving Distinguished from Withdrawal Symptoms

*by Kenneth J. Bender, Pharm.D., M.A.**Psychiatric Times • September 1995 • Vol. XII • Issue 9*

Drug craving is inextricably linked with drug abuse and withdrawal. But the sensation of craving has eluded assessment and any certainty about whether it drives or arises from drug use. Researchers at the Cincinnati Veterans Affairs Medical Center presented three reports on their efforts to understand drug craving and its implications for drug abuse treatment at the recent 148th Annual American Psychiatric Association Meeting. The group sought to differentiate drug craving from withdrawal symptoms, distinguish between craving intensity for different drugs, and gauge the impact of inpatient chemical dependence treatment on both craving and psychiatric symptomatology.

Juris Mezinskis, Ph.D., director of Substance Abuse Quality Improvement, explained that the impetus for studying craving began in 1991. At that time the Substance Abuse Treatment Program administrative staff decided to develop an empirically based program in which all measures which were normally given for clinical reasons, would also be entered in a computerized data base for quality improvement and research purposes. Through the efforts of Eugene Somoza, M.D., Ph.D., director of substance abuse treatment; Sue Dyrenforth, Ph.D., director of substance abuse rehabilitation; Mark Cohen, Ph.D., chief, psychology service, and others, an infrastructure was established to collect a data base which currently contains addiction severity index scores and other measures for more than 1,300 patients. The craving data presented at the APA is a subset of this clinical data base.

WHO Defines Craving

The Cincinnati VA research was preceded by national and international efforts to develop a consensus on the nature of drug craving. In 1991, the Addiction Research Center of the National Institute on Drug Abuse (NIDA) convened a conference to consider whether the concept of drug craving warranted further research, and whether efforts to quell craving might ultimately improve drug abuse treatment.

The NIDA consensus statement described the disparity of views on drug craving. "These differences range from the extremes of



Most Po
Medica
Sleep
Unders
Dynam
Relativ
Traum
Behavi
Sexual

Most Er
Under:
Dynam
Relativ
Traum
Behavi
Sexual
The Re
Abuse
Violenc

Clinical
AIMS (
Moven
BPRS (R
Rating
MDQ (Q
Questi
All Sca

(ECT)

Impulse Control Disorders

Mood Disorders

Obsessive Compulsive Disorder

Panic Disorder

Personality Disorders

Post Traumatic Stress Disorder (PTSD)

Psychotherapy

Relationship Issues

Schizophrenia

Sexual Issues

Somatoform Disorders

Substance Abuse

Suicidal Behavior

Violence

Women

Workplace

Supporter Resources

Media Kit

Classified/Online Advertising Rates

Display Ad Rates/Sizes

those who believe craving is the major determinant of drug-taking behavior, to those who believe that craving is an epiphenomenon or hypothetical construct that should be ignored in scientific investigations." The statement elaborated, "There is also no standardized methodology for measuring craving or even a general agreement about how to develop psychometrically sound indices."

The participants, who were experts from several disciplines, agreed that craving in humans is a subjective state that is associated with drug dependence, but called for a substantial research effort (Pickens and Johanson 1992).

The following year, the United Nations International Drug Control Programme (UNDCP) and the World Health Organization (WHO) organized an Expert Committee to define the term *craving*, to review the scientific status of the concept and to encourage further clinical and preclinical research.

The UNDCP-WHO Expert Committee framed a broad definition for drug craving, as "the desire to experience the effects of a previously experienced psychoactive substance" (UNDCP and WHO 1992). This effort was a decided improvement over their previous attempt 40 years prior, which, according to Mezinskis, "was generally rejected by the scientific community." Their recommendation then was to abandon the term *craving* because of the confusion surrounding it, in favor of the two terms, *physical dependence* and *pathological desire* (WHO 1955).

The UNDCP-WHO has now elaborated on their broad definition of drug craving and called for a review of theoretical constructs which might support experimental investigation of the phenomenon. In response, Athina Markou, Ph.D., and colleagues at the department of neuropharmacology, Scripps Research Institute, La Jolla, Calif., considered the experimental data on craving within the framework of incentive-motivational theories of behavior, and examined possible animal models.

Markou pointed out, "It should be recognized that drug craving is a multidimensional phenomenon that consists of subjective, behavioral, physiological and neurochemical correlates" (Markou, et al. 1993).

Markou's group indicated they expect the physiologic processes underlying drug craving to have behavioral expression. "Thus, behavioral measures, in addition to providing a detailed characterization of the behavioral components of craving, could also provide an accurate reflection of the neurobiological aspects...and allow the study of these physiological and neurochemical mechanisms."

Craving vs. Withdrawal

These soundings below the deceptively familiar surface of drug craving indicate ample depth for researchers to plumb. Cincinnati VA researchers began by determining whether drug craving could be distinguished from other negative feelings associated with withdrawal (Mezinskis 1995). They acknowledged and tested the possibility that "craving" might be a nonspecific description used by drug-dependent individuals to refer to their withdrawal discomfort and general psychological distress.

In reviewing drug detoxification literature, Somoza identified eight symptoms generally associated with drug withdrawal: anxiety, depression, restlessness, anger, irritability, frustration, impatience and poor concentration. A total of 376 patients in a VA 28-day inpatient chemical dependence program were then



Identified over a one-year period and instructed to use a four-point scale to self-rate the severity of any such symptoms they experienced during drug withdrawal. They used the same scale to also rate the intensity and frequency of their drug craving. Factor analysis of the resulting 5,867 daily ratings evidenced clear differentiation between withdrawal symptoms and drug craving.

All of the drug craving ratings loaded on one factor and all of the psychological distress symptoms loaded on the second factor allowed Mezinskis to conclude that craving is a separate phenomenon.

Mezinskis indicated that as craving and psychological distress appear distinct, treatment regimens might appropriately address each:

"Cue extinction procedures and behavioral procedures like that probably should be used (for craving)," said Mezinskis. The researchers also assume that pharmacologic agents can directly attenuate craving and are now conducting an open trial of naltrexone (ReVia) in its recent FDA-approved indication for alcohol-dependent patients; as well as a double-blind study of its effect on craving in cocaine dependent patients.

Quantifying Craving

Somoza described the group's effort to further quantify craving intensity in their 376 subjects, and ascertain whether different drugs prompt different craving levels (Somoza, et al. 1995). The researchers compared intensity ratings for different drugs in patients who craved at least two drugs. Patient ratings were then divided into groups based on the top two drugs of choice. In other words, there were 1,258 ratings in the sample for which cocaine and alcohol were the top two drugs of choice. Of these, 811 ratings listed cocaine as more intensely craved than alcohol, and 447 ratings listed alcohol as more intensely craved than cocaine.

"This would suggest that cocaine is more intensely craved than alcohol by a ratio of 1.8 to 1," Somoza and Mezinskis said.

The researchers identified as the drug preference ratio (DPR) as the ratio of the craving for the first drug to the second. The resulting DPRs were: cocaine/alcohol, 1.81; opiates/cocaine, 1.32; and cocaine/marijuana, 18.4.

From these ratios, a drug-craving scale was constructed with marijuana assigned a value of 1.0. The respective levels of craving for alcohol, cocaine and opiates were 10.2, 18.4 and 24.3 (see **Figure**). Somoza qualified these relative values as derived from small patient populations, and indicated he is now cross-validating them on new patient samples.

Others have also wondered about differences in the craving for different drugs. The question was prominent in the recent debates over the addictive nature of nicotine and intensity of nicotine craving (PT, September 1994). Nonsmoking activists are wont to compare smokers' craving to narcotic addiction, despite the lack of comparative data.

A British group did compare cigarette and opiate craving in the early stages of abstinence. In 24 patients seeking treatment for nicotine dependence and another 24 for opiates, the latter group was found statistically to have reported stronger feelings on all dysphoric items (Gossop, et al. 1990). Rank ordering showed significant correlation of "tension," "anxiety" and "restlessness" among both nicotine and narcotic users. Neither group rated "excited" or "curious" as relevant to their craving experience.

The British researchers noted that both smokers and narcotic users judged their craving experience to be unpleasant. Theirs was an aversive sensation, in contrast to some theories that craving is "appetitive or positive in nature" (Marlatt and Gordon 1985). Somoza indicated that his group's experience supports the notion that craving is unpleasant, having to be differentiated from discomforting withdrawal symptoms.

Somoza found that nicotine craving in the VA population was very intense, and difficult to quantify or compare with the craving for other drugs.

"Most drugs (appeared) qualitatively the same, but quantitatively different," said Somoza. "The only exception was nicotine." He added, "The craving for nicotine came out qualitatively different compared to the craving for alcohol, opiates and cocaine."

Somoza speculated that the unique craving for nicotine may have manifested because cigarettes were the only dependency-producing drug allowed during the program.

Susan Dyrenforth, Ph.D., presented the group's assessment of the program's effectiveness in reducing both drug craving and psychological distress (Dyrenforth and colleagues 1995). She noted that previous studies have shown that supportive treatment and milieu reduces depression and other psychiatric symptomatology. To compare changes in psychiatric symptomatology with changes in craving for various drugs of abuse, the group correlated the ratings of the eight withdrawal symptoms and of craving intensity across the 28 days of inpatient treatment.

As other successful treatment programs have found, the VA group reported that psychiatric symptoms were significantly reduced as a function of the number of treatment days. Drug craving also decreased over time, with each drug class evidencing a different craving decrement. Craving for alcohol and cocaine decreased at a faster rate than did psychiatric symptoms. Patients whose craving for drugs remained high at the end of treatment were found to be those who had higher psychiatric composite scores on the Addiction Severity Index at the beginning of treatment. The researchers concluded that inpatient treatment significantly reduces drug craving, but that continued craving is associated with preexisting psychiatric symptomatology. In further studies, they plan to follow these patients to determine if they are at higher risk for relapse.

References

1. Dyrenforth SR, Mezinskis J, Cohen M, et al. Changes in drug craving during inpatient chemical dependence treatment. Presented at the 148th Annual American Psychiatric Association Meeting. May 25, 1995. Miami Beach, Fla.
2. Gossop M, Powell J, Grey S, Hajek P. What do opiate addicts and cigarette smokers mean by "craving"? A pilot study. *Drug Alcohol Depend.* 1990;26(1):85-87.
3. Markou A, Weiss F, Gold LH, et al. Animal models of drug craving. *Psychopharmacology (Berl).* 1993;112(2-3):163-182.
4. Marlatt A, Gordon J. *Relapse Prevention.* New York: Guilford Press; 1985.
5. Mezinskis J, Somoza EC, Dyrenforth SR. Drug craving versus withdrawal symptoms: Are they different? Presented at the 148th Annual American Psychiatric Association Meeting, May 25, 1995; Miami Beach, Fla.

6. Pickens RW, Johanson CE. Craving: Consensus of status and agenda for future research. *Drug Alcohol Depend.* 1992;30 (2):127-131.
7. Somoza EC, Dyrenforth SR, Goldsmith J, et al. In search of a universal drug craving scale. Presented at the 148th Annual American Psychiatric Association Meeting. May 25, 1995; Miami Beach, Fla.
8. UNDCP and WHO Informal Expert Committee on the Drug-Craving Mechanism. Report, United Nations International Drug Control Programme and World Health Organization; 1992. Technical report series (No. V. 92-54439 T).
9. WHO Expert Committees on Mental Health and on Alcohol. The "craving" for alcohol. *QJ Studies Alcohol.* 1955;16:33-66.

[Email this page to a friend](#)

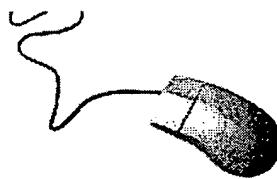
[Print this article](#)

What Do You Think About...?

Is the use of antidepressants in bipolar disorder:

- Effective and largely safe.
- Largely ineffective and mostly unsafe.

[Vote](#)



Assess Your Level of Knowledge on **Bipolar Disorder**

[CancerNetwork](#) | [ConsultantLive](#) | [Diagnostic Imaging](#) | [Psychiatric Times](#) | [Applied Neurology](#)

Copyright © 2006 CMP Healthcare Media Group LLC, a United Business Media company
[Privacy Statement](#) | [Terms of Service](#)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record.**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.